Selection of Patients with Advanced-stage Cervical Cancer for Para-aortic Lymphadenectomy in the Era of PET/CT

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Abstract. *Background: The aim of this study was to report the false-negative rate of positron-emission tomography (PET) /Computed Tomography (CT) for para-aortic (PA) lymph node (LN) metastasis and to examine if PA lymphadenectomy could be omitted when PET/CT of the pelvic area is negative. Patients and Methods: Patients without evidence of extrapelvic disease on preoperative imaging or in the PA area were included. Each patient underwent a laparoscopic PA lymphadenectomy. Results: A total of 61 patients were included. Seven patients (11%) had PALN metastasis. The false-negative rate of PET/CT was 11%. When PET/CT was positive for pelvic nodes, the risk for PA metastasis was 18% versus 8% when PET/CT was negative in the pelvic area (p=0.24). Conclusion: The apparent low sensitivity of the PET/CT does not make it a relevant alternative to surgical LN staging when no uptake is visualized in the PA area. However, for patients in whom PET/CT is negative in the pelvic area, the risk of metastasis in the PA area is low.*

Classically, locally advanced cervical cancer (LACC) [stage IB2 or higher, according to the International Federation of Gynaecology and Obstetrics (FIGO) classification] are treated with a combination of external irradiation and brachytherapy with concurrent chemotherapy (1). This combination has proven its efficacy on progression-free and overall survival (1) and is considered as the standard treatment for bulky cervical cancer by most North American and Western European teams (2). Usually, whatever the pelvic node status is, pelvic nodes are included in radiation fields and receive a local boost when necessary (2). The pelvic radiation field is widened to the para-aortic (PA) area if metastases in this region are likely upon imaging, or proven by pathological examination. The PA lymph node (LN) staging can be performed by radiology and/or by surgery, but surgical staging remains the gold standard. Ideally, non-invasive methods to evaluate metastasis in PALN are required. New imaging techniques such as 18-fluorodeoxyglucose (18-FDG) positron-emission tomography (PET)/computed tomography (CT) have been developed. An uptake of 18-FDG at the PA level on PET/CT is associated with a high probability of LN metastasis (3). In such cases, extension of radiation fields to cover the PA area is indicated without histological examination of LNs (4). The aim of this study was to report the false-negative rate of PET/CT for PALN metastasis and to examine if PA lymphadenectomy could be omitted when PET/CT of the pelvic area is negative, as previously suggested (5).

Patients and Methods

Study population. We conducted a retrospective multicenter analysis of consecutive untreated patients with histologically-confirmed FIGO stage IB2-IVA invasive cervical carcinoma, managed in three French institutions: Lariboisiere, Bichat and Beaujon hospitals between April 2006 and December 2011. Each patient had a pre-therapeutic assessment, which included an abdomino-pelvic magnetic resonance imaging (MRI) and a PET/CT. The size of the tumor was assessed on the MRI examination. Only patients without

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Key Words: Locally advanced cervical cancer, PET/CT, para-aortic lymphadenectomy, staging.

surgical contraindications and no evidence of extrapelvic disease on preoperative imaging (MRI or CT scan) or in the PA area on PET/CT were included. Each patient underwent laparoscopic surgical staging with a PA lymphadenectomy.

PET/CT imaging protocol. After at least six hours of fasting, patients were injected intravenously with 185-370 mBq of radionuclide (18-FDG). After 60 min, rest and bladder voiding, a hybrid PET/CT system combining a third-generation multislice spiral CT with a PET was performed. All PET/CT images were evaluated by experienced nuclear medicine and radiology physicians. Because standard uptake values are variable among patients and are not reproducible among institutions (6), only the presence of a pathological uptake was considered as positive.

Surgical technique. All the surgical procedures were performed by experienced gynaecological surgeons who were aware of the PET/CT findings prior to the LN dissections. All the surgical procedures included an extra- or transperitoneal laparoscopic lymphadenectomy. The choice of the route, extraperitoneal or transperitoneal was decided by the surgeon. The upper limit of PALN dissection was the left renal vein. Clips were set up at the level of the superior limit of the PA lymphadenectomy to guide radiotherapy. Several patients had sentinel LN biopsy. If this was positive, the lymphadenectomy was interrupted, but if it was negative, PA lymphadenectomy was performed. LNs of each area were separately extracted in a protected manner.

Histopathological evaluation. LNs were submitted to routine sectioning and pathological evaluation. On each block, five haematoxylin and eosin (H&E)-stained slides were cut at 40 μm intervals and three unstained slides were cut at each level. If all five levels were negative by H&E staining, the case was submitted for immunohistochemical analysis. LN macrometastasis was defined larger than 2 mm and a micrometastasis as smaller than 2 mm.

Statistical analysis. The value of preoperative PET/CT was assessed by estimating the false-negative rate, calculated by dividing the number of patients with histologically-proven positive LN with negative PET/CT by the total number of patients with negative PET/CT for the PA area.

Morbidity of the surgical staging. Morbidity of the pelvic and PA lymphadenectomies was studied by the complications during the surgery and the complications one month after the surgery. The complications were analyzed according to the Clavien-Dindo classification (7).

Results

Between April 2006 and December 2011, 61 patients were included in the study. The clinical and pathological characteristics of the 61 patients are summarized in Table I. The median delay between the MRI and the surgical staging and between the PET/CT and the laparoscopy were 9 (range=3-15) and 8 (range=2-17) days, respectively. Eight patients underwent a PA lymphadenectomy by the retroperitoneal route and 53 by transperitoneal route. One of the two patients who had a sentinel LN biopsy, had a positive sentinel LN at the PA level and consequently did not undergo complete PA lymphadenectomy. The median number of LNs taken during the PA lymphadenectomy was 13 (range=2-42). Seven patients (11%) had at least one PALN metastasis. The false-negative rate of PET/CT in this study was 11% (seven out of 61 patients with PET/CT). The median number of metastatic PALNs was 3 (range=1-14). The size of the LN was always greater than 2 mm (*i.e.* macrometastasis).

Table II summarizes the pathological results. Among the seven patients falsely-negative in the PET/CT, three had LN metastasis of 10 mm and four had LN metastases with a size of between 4 and 8 mm. When PET/CT was positive for pelvic nodes, the rate for PA metastasis was 18% *versus* 8% when PET/CT was negative in the pelvic area (p=0.24). Table III summarizes the complications that occurred during surgery and within one month following the PA lymphadenectomy. Four patients had a grade I complication, one patient presented a grade II complication, two patients had a grade III complication (one section of the left ureter and one an intestinal obstruction) and one patient had a grade IV complication (cardiac decompensation requiring a stay in a recovery unit for 24 hours).

Discussion

Between 15% and 30% of patients with LACC have PALN involvement (8). It constitutes the most important risk factor associated with poor survival (9). Due to intestinal morbidity, oncologists are reluctant to systematically include this field for radiation therapy unless PALN metastasis has been proven (10). The gold standard for LN staging is PA lymphadenectomy by laparoscopy. Although this technique has been reported as "feasible" and "secure" (11), it remains an invasive surgical technique, with potential intraoperative and postoperative complications. Unfortunately, conventional imaging (CT scan and MRI) cannot predict PA involvement (12, 13). PET/CT is a functional test of the glycolytic activity of the tumour and the relative deficiency of glucose-6-phosphate in tumour cells. It has been extensively studied in solid tumours and, for over ten years now, in cervical cancer. Rose *et al*. (14) were the first to report the interest of the PET/CT for patients with LACC. They found a high sensitivity (75%) and specificity (92%) of 18-FDG uptake in metastatic LNs. Since the first studies were published, several studies have suggested that PET/CT is not as successful, in the detection of LN metastases, as initially expected. Recently Leblanc *et al*. (19) reported that sensitivity of PET/CT for the detection of PA metastasis was only 33% and there was a high rate of false-negatives (66%). In the present study, the rate of false-negatives was 11%. False-negative rates constitute important data for clinicians since they reflects the number of patients who would be under-staged and thus under-treated. The small size of these LNs could explain the high rate of false-negatives of PET/CT.

Table I. *Clinicopathological characteristics of 61 patients.*

Characteristic		Histological	
	(n=61)	PA+ (n=7)	PA– (n=54)
Median age (years)	48	51	47
Range	27-78	29-69	27-78
Histological type			
Squamous carcinoma	49	4	45
Adenocarcinoma	8	2	6
Small-cell carcinoma	1	0	1
Mixted carcinoma	3	1	2
Menopausal	29	3	26
FIGO stage			
IB2	11	1	10
IIA	14	1	13
IIB	30	4	26
IIIA	1	0	1
IIIB	3	0	3
IVA	2	1	1

PA: Para-aortic; FIGO: International Federation of Gynaecology and Obstetrics.

Table II. *The results of the positron-emission tomography/computed tomography (PET/CT) at the pelvic level according to histological presence of para-aortic (PA) disease.*

Pelvic PET/CT	PA+	PA–	Total
Negative	3	36	39
Positive	4	18	22
Total	7	54	61

Table III. *Morbidity of lymphadenectomy.*

Morbidity	n (%)
Ureter injury	1 (2%)
Nerve injury	1 (2%)
Lymphocyst	3 (4%)
Venous thrombosis	1 (2%)
Intestinal obstruction	1 (2%)
Decompensation of a chronic disease	1 (2%)
Hospital stay (days)	
Median	5
Range	3-25

Indeed, PET/CT has a better diagnostic performance for LNs with a size of 10 mm or more (15, 16). These data could explain why, in the present study, LNs with a size smaller than 5 mm were not detected by PET/CT. Moreover, this study was retrospective and PET/CT was interpreted only once, without review. This could explain the high rate of false-negatives in retrospective studies and, comparatively, the better results of a prospective study (17, 18).

According to Uzan *et al*. (5), if the PET/CT is negative in the pelvic area, the need of a PA lymphadenectomy could be questioned because of a very low risk of PA involvement (24% *versus* 2.9%). The overall rate of PALN metastasis with no uptake on the PET/CT (false-negative rate) in the literature is 12% (4). The rate of patients with PA metastasis and with positive pelvic nodes on PET/CT was 22% in the review by Gouy *et al*. (5) and 18% in the present study, higher than the overall false-negative rate of 12% in the literature. In the present study, 8% of the patients had PA metastasis with a negative pelvic node PET/CT status. Our results are consistent with the findings of Uzan *et al*. (6) but nevertheless less frank. If this strategy (no PA lymphadenectomy when PET/CT is negative in the pelvic area) was applied, we would have undertreated 8% of the patients. The question is what rate of false-negatives can be accepted in order to avoid unnecessary PA lymphadenectomy? The rate of false-negatives should be balanced against the rate of complications of PA lymphadenectomy. In the literature, complication rates of PA lymphadenectomy by laparotomy range from 10% to 19% (19) and the laparoscopic approach is associated with a lower complication rate of 7% (11, 20, 21).

Conclusion

PET/CT is a relatively new imaging procedure for detecting pelvic and PALN metastases in LACC. Surgical staging in patients with an uptake in the PA area on the PET/CT could be avoided because of the high specificity of the PET/CT. The low sensitivity of PET/CT does not make it a relevant alternative to surgical LN staging when no uptake is visualized in the PA area, except for these patients with a negative pelvic node status on PET/CT. Nevertheless, the therapeutic impact of PA surgical staging (in patients with a negative PET/CT result in the PA area) remains controversial and the only way to confirm its therapeutic value would be to conduct a randomized trial.

References

1 Rotman M, Pajak TF, Choi K, Clery M, Marcial V, Grigsby PW, Cooper J and John M: Prophylactic extended-field irradiation of para-aortic lymph nodes in stages IIB and bulky IB and IIA cervical carcinomas. Ten-year treatment results of RTOG 79-20. JAMA *274*: 387-393, 1995.

2 Vale C, Tierney JF, Stewart LA, Brady M, Dinshaw K, Jakobsen A, Parmar MK, Thomas G, Trimble T, Alberts DS, Chen H, Cikaric S, Eifel PJ, Garipagaoglu M, Keys H, Kantardzic N, Lal P, Lanciano R, Leborgne F, Lorvidhaya V, Onishi H, Pearcey RG, Pras E, Roberts K, Rose PG, Thomas G and Whitney CW. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. J Clin Oncol *26*: 5802-5812, 2008.

3 Leblanc E, Gauthier H, Querleu D, Ferron G, Zerdoud S, Morice P, Uzan C, Lumbroso S, Lecuru F and Bats AS: Accuracy of 18-fluoro-2-deoxy-D-glucose positron-emission tomography in the pre-therapeutic detection of occult para-aortic node involvement in patients with a locally advanced cervical carcinoma. Ann Surg Oncol *18*: 2302-2309, 2011.

4 Gouy S, Morice P, Narducci F, Uzan C, Gilmore J, Kolesnikov-Gauthier H, Querleu D, Haie-Meder C and Leblanc E: Nodal-staging surgery for locally advanced cervical cancer in the era of PET. Lancet Oncol *13*: e212-220, 2012.

5 Uzan C, Souadka A, Gouy S, Debaere T, Duclos J, Lumbroso J, Haie-Meder C and Morice P: Analysis of morbidity and clinical implications of laparoscopic para-aortic lymphadenectomy in a continuous series of 98 patients with advanced-stage cervical cancer and negative PET-CT imaging in the para-aortic area. Oncologist *16*: 1021-1027, 2011.

6 Visser EP, Philippens ME, Kienhorst L, Kaanders JH, Corstens FH, de Geus-Oei LF and Oyen WJ: Comparison of tumor volumes derived from glucose metabolic rate maps and SUV maps in dynamic ^{18}F-FDG PET. J Nucl Med *49*: 892-898, 2008.

7 Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, de Santibanes E, Pekolj J, Slankamenac K and Bassi C: The Clavien-Dindo classification of surgical complications: Five-year experience. Ann Surg *250*: 187-196, 2009.

8 Lagasse LD, Creasman WT, Shingleton HM, Ford JH and Blessing JA: Results and complications of operative staging in cervical cancer: Experience of the Gynecologic Oncology Group. Gynecol Oncol *9*: 90-98, 1980.

9 Tseng JY, Yen MS, Twu NF, Lai CR, Horng HC, Tseng CC, Chao KC and Juang CM: Prognostic nomogram for overall survival in stage IIB-IVA cervical cancer patients treated with concurrent chemoradiotherapy. Am J Obstet Gynecol *202*: 171-177, 2010.

10 Varia MA, Bundy BN, Deppe G, Mannel R, Averette HE, Rose PG and Connelly P: Cervical carcinoma metastatic to para-aortic nodes: Extended field radiation therapy with concomitant 5-fluorouracil and cisplatin chemotherapy: A Gynecologic Oncology Group study. Int J Radiat Oncol Biol Phys *42*: 1015-1023,1998.

11 Dargent D, Ansquer Y and Mathevet P: Technical development and results of left extraperitoneal laparoscopic para-aortic lymphadenectomy for cervical cancer. Gynecol Oncol *77*: 87-92, 2000.

12 Bipat S, Glas AS, van der Velden J, Zwinderman AH, Bossuyt PM and Stoker J: Computed tomography and magnetic resonance imaging in staging of uterine cervical carcinoma: A systematic review. Gynecol Oncol *91*: 59-66, 2003.

13 Hancke K, Heilmann V, Straka P, Kreienberg R and Kurzeder C: Pretreatment staging of cervical cancer: Is imaging better than palpation? Role of CT and MRI in preoperative staging of cervical cancer: Single institution results for 255 patients. Ann Surg Oncol *15*: 2856-2861, 2008.

14 Rose PG, Adler LP, Rodriguez M, Faulhaber PF, Abdul-Karim FW and Miraldi F: Positron-emission tomography for evaluating para-aortic nodal metastasis in locally advanced cervical cancer before surgical staging: A surgicopathologic study. J Clin Oncol *17*: 41-45, 1999.

15 Roh JW, Seo SS, Lee S, Kang KW, Kim SK, Sim JS, Kim JY, Hong EK, Cho DS and Lee JS: Role of positron emission tomography in pretreatment lymph node staging of uterine cervical cancer: A prospective surgicopathologic correlation study. Eur J Cancer *41*: 2086-2092, 2005.

16 Sironi S, Buda A, Picchio M, Perego P, Moreni R, Pellegrino A, Colombo M, Mangioni C, Messa C and Fazio F: Lymph node metastasis in patients with clinical early-stage cervical cancer: Detection with integrated FDG PET/CT. Radiology *238*: 272-279, 2006.

17 Reinhardt MJ, Ehritt-Braun C, Vogelgesang D, Ihling C, Hogerle S, Mix M, Moser E and Krause TM: Metastatic lymph nodes in patients with cervical cancer: Detection with MR imaging and FDG PET. Radiology *218*: 776-782,2001.

18 Lin WC, Hung YC, Yeh LS, Kao CH, Yen RF and Shen YY: Usefulness of (18)F-fluorodeoxyglucose positron-emission tomography to detect para-aortic lymph nodal metastasis in advanced cervical cancer with negative computed tomography findings. Gynecol Oncol *89*: 73-76,2003.

19 Moore KN, Gold MA, McMeekin DS, Walker JL, Rutledge T and Zorn KK: Extraperitoneal para-aortic lymph node evaluation for cervical cancer via pfannenstiel incision: Technique and peri-operative outcomes. Gynecol Oncol *108*: 466-471, 2008.

20 Gil-Moreno A, Franco-Camps S, Cabrera S, Perez-Benavente A, Martinez-Gomez X, Garcia A, and Xercavins J: Pre-therapeutic extraperitoneal laparoscopic staging of bulky or locally advanced cervical cancer. Ann Surg Oncol *18*: 482-489, 2011.

21 Tillmanns T and Lowe MP: Safety, feasibility, and costs of outpatient laparoscopic extraperitoneal aortic nodal dissection for locally advanced cervical carcinoma. Gynecol Oncol *106*: 370-374, 2007.

Received October 6, 2012
Revised November 6, 2012
Accepted November 7, 2012